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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Schwegman, Lundberg, Woessner & Kluth, P.A.
P.O. Box 2938
Minneapolis, MN 55402

EXAMINER	
KERR, KATHLEEN M	12

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/775,938	HAYGOOD ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66-89* is/are pending in the application.

4a) Of the above claim(s) *75-85 and 89* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66-74 and 86-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (Paper No. 9, mailed on September 12, 2002), Applicants filed an election received on December 9, 2002 (Paper No. 11). Claims 66-89 are pending in the instant Office action.

Election

2. Applicant's election with traverse of Group 19, Claims 66-74 and 86-89 related to SEQ ID NO:37, in Paper No. 11 is acknowledged. The traversal is on the ground(s) that SEQ ID NOs:29-37 are closely linked in the genome of *Endobugula* and together these sequences form a primary structure corresponding to that of a polyketide synthase (PKS). This is not found persuasive because while the sequences may be spatially linked in the *Endobugula* genome, this does not render them related. Moreover, while they may all be involved in encoding a PKS for bryopyran, they each encode distinct enzymes with distinct and independent functions in the bryopyran PKS pathway. For these reasons, each of the different sequences encoding different enzymes in the pathway are distinct. Applicants also argue that no search burden exists to examine all the Groups together. This is not the case. While the class/subclass maybe be the same search in the patent databases, each independent SEQ ID NO must be separately searched in commercial databases and those results separately evaluated; none of these searches are co-extensive. Applicants argue that the cost is prohibitive; this is not a valid argument considering that the criteria for restriction are independent and/or distinct inventions.

The requirement is still deemed proper and is therefore made FINAL.

Claims 66-89 are pending. Claims 75-85 are withdrawn from further consideration as non-elected inventions. Claim 89 is drawn wholly to non-elected subject matter because SEQ ID NO:37 does not encode any of the named polypeptides; thus, Claim 89 is also withdrawn from further consideration here. Claims 66-74 and 86-88, as they related to SEQ ID NO:37 ONLY, will be examined herein.

Priority

3. The instant application is granted the benefit of priority of a continuation of the international application PCT/US00/21326 filed on August 4, 2000 as requested in the declaration and the first lines of the specification.

The instant application is also granted the benefit of priority for the U.S. Provisional Application No. 60/147,283 filed on August 4, 1999 as requested in the declaration and the first lines of the specification. The Examiner notes that the elected SEQ ID NO:37 is NOT disclosed in this priority document.

Information Disclosure Statement

4. The information disclosure statement filed on January 7, 2002 (Paper No. 8) has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy. The Examiner has deleted the web page reference from one of the citation for clarity; no action is required by Applicants.

Compliance with the Sequence Rules

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2).

However, this application fails to **fully** comply with the requirements of 37 C.F.R. § 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

a) Figure 14B has a DNA and an amino acid sequence disclosed without benefit of a SEQ ID NO.

b) Figure 15B has two DNA sequence contigs disclosed without benefit of a SEQ ID NO.

c) Figure 16B has a DNA disclosed without benefit of a SEQ ID NO.

d) Figure 17B has four DNA sequences disclosed without benefit of a SEQ ID NO.

e) Figure 18B has one DNA sequence disclosed without benefit of a SEQ ID NO.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Objections to the Specification

6. The specification is objected to because the title is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01). The Examiner suggests the following new title:

---Polynucleotides Encoding a Bryopyran Polyketide Synthase---

7. In the specification, the Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of the source species of the disclosed polynucleotides for completeness.

8. The specification is objected to for the following confusing and/or incomplete issues:

a) Figure 22T notes SEQ ID NO:11 (which is a DNA sequence in the sequence listing); however an amino acid sequence is disclosed.

b) Figures 22AA and 22BB both label the amino acid sequences, which are different, SEQ ID NO:24; one of these two labels must be incorrect.

c) On pages 5-6, the descriptions of Figures 14-18 must present the descriptions of A and B in separate paragraphs, as separate figures. Also, SEQ ID NOs can be added here to overcome the above sequence compliance issue.

d) On page 71, line 30, no page number is noted for the Ways *et al.* (1995) reference.

Appropriate correction is required.

Claim Objections

9. Claims 66-74 and 86-88 are objected to for containing non-elected subject matter. Said claims will be examined herein as if they have been limited to relating to SEQ ID NO:37.

10. Claims 69-74 are objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to

cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The instant claims attempt to further limit the parent claim, Claim 66, by requiring additional limitations on the marine organism in Claim 66. However, due to the lack of clarity of the term "derived from", as noted below, these additional phrases do not add *real* limitations on the claimed subject matter.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 66-74 and 86-87 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "at least one polypeptide that catalyzes at least one step in the synthesis of at least one polyketide or bryopyran ring" is wholly unclear as to its metes and bounds. Must the polypeptide directly catalyze the production of a polyketide or a bryopyran ring-containing compound? Or more broadly, must the polypeptide only directly catalyze reactions in the biosynthetic pathways of polyketides and/or bryopyran-ring containing compounds? If so, these pathways, with their numerous precursors, must be defined to clearly define the metes and bounds of the claimed subject matter. Clarification is required.

Additionally, the instant claim is unclear in view of the elected subject matter, relating to SEQ ID NO:37, since ***no encoded polypeptides*** are defined from SEQ ID NO:37 and, more particularly, no polyketide synthase polypeptides are described as being encoded by SEQ ID NO:37. SEQ ID NO:37 is only defined as the sequence of 5B Pst A7 contig (see page 60).

Thus, all claims relying on encoding a particular function are unclear in view of the instant specification.

12. Claims 66-74 and 86-87 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 66, the phrase "derived from" is unclear as to its metes and bounds. Must the claimed polynucleotide composition be native to a marine organism? Or more broadly, if a sequence is a polynucleotide, naturally occurring in a marine organism but then recombinantly altered (or derived) to be another polynucleotide, is this sequence encompassed? The phrase is entirely unclear since it implies one limitation while, broadly but reasonably interpreted, can mean something significantly broader.

13. Claims 66-74 and 86-87 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 66, the phrase "marine organism" is unclear as to its metes and bounds. Must the organism *only* live in an aquatic environment to be a "marine organism"?

Moreover, particularly the Claims 70-74 are confusing as to the origin of the PKS genes themselves, whether they be from the *Bugula neritina* marine fungus or the proteobacterium symbiont *Candidatus endobugula sertula*. Recent publications indicate that the genes are not from the fungus (see Davidson *et al.* 2001) rendering Claims 73 and 74 specifically unclear. Moreover, it is unclear if this proteobacterium, living within a marine fungus, is considered a "marine organism". Clarification is required.

14. Claims 86-87 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The terms "moderate hybridization" and "stringent hybridization" are unclear. On page 9, an exemplary definition of stringent conditions is disclosed; however, no clear definition is named therein. No definition of moderate conditions is disclosed. The art contains various definitions of stringent and moderate hybridizations conditions. Without a clear definition of hybridization conditions, in either the specification or the art, the terms are unclear. Clarification is required.

15. Claims 86-87 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear how the complement of the purported encoding sequences can encode a polypeptide having the purported function in Claim 66. The Examiner suggests writing independent claims that incorporate the function of Claim 66 such that the claimed complement sequence need not have the function.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 66-74 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 66 is drawn to a polynucleotide composition that is claimed solely by a function of an encoded polypeptide, albeit an *unclear function* as noted above, and *without any structural limitations*.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, the elected subject matter of SEQ ID NO:37 is described as the sequence of contig 5B Pst A7 that is involved in encoding polyketide synthase and/or bryopyran ring-containing compounds. No open reading frames are noted; thus SEQ ID NO:37 is not described as encoding a particular polypeptide. Moreover, this sequence is only described according to the putative and broad functional characteristics of the undescribed polypeptides SEQ ID NO:37 is purported to encode; no structural relationship is described or used in the

claims. Thus, one of skill in the art would be unable to predict the structure of members of this genus, other than SEQ ID NO:37 exactly, by virtue of the instant disclosure. Therefore, claims drawn to polynucleotide compositions are not adequately described.

17. Claims 86-87 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 86-87 are drawn to polynucleotides structurally related to SEQ ID NO:37 by virtue of hybridization conditions (albeit unclear conditions as noted above). However, the functional limitation in Claim 66 is unclear. Thus, Claims 86-87 are drawn to polynucleotide products having a *varied structure* with *no clear, functional limitation.*

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical

characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

The instant specification discloses polynucleotide SEQ ID NO:37 as being the entire sequence of contig 5B Pst A7 that putatively encodes polyketide synthases and/or bryopyran ring-containing synthases (although no open reading frames or clear functions of encoded polypeptides are defined). Applicants may have fully described the genus relating to said SEQ ID NO with both sequence identity limitations (hybridization conditions) and functional limitations (as noted above, the polyketide synthase functionality described is unclear). However, the genus of the instant claims also contains polynucleotides within the sequence identity limitations, but having different function. The specification has not fully described a genus that has sequence identity limitations in the absence of functional limitations.

Claim Rejections - 35 U.S.C. § 101

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

18. Claims 66-74 and 86-88 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific, asserted utility or a well established utility. To fulfill the utility requirement of 35 U.S.C. § 101, an invention must have a specific, substantial, and credible utility that is disclosed in the specification or which is well established as considered by one of ordinary skill in the art.

The instant specification discloses polynucleotide SEQ ID NO:37 as being the entire sequence of contig 5B Pst A7 that, by implication, putatively encodes polyketide synthases and/or bryopyran ring-containing synthases. The field of polyketide synthases, both modular and aromatic, is well-studied. Polyketide synthases are multifunctional, domain-containing enzymes that catalyze numerous, distinct catalytic reactions on their different domains using numerous, distinct precursor compounds.

The instant specification describes experiments that utilize probes drawn from ketosynthase domains of modular polyketide synthase genes to clone SEQ ID NO:37; ketosynthase domains are a particular functionality of a multifunctional polyketide synthase protein. No open reading frames and/or encoded proteins are defined for SEQ ID NO:37. No specific function, such as encoding a ketosynthase-functioning enzyme, is proposed for SEQ ID NO:37. No tested functionality of SEQ ID NO:37 is offered, for example, transformation into a bryopyran-minus strain and screening for the introduction of the ability to produce bryopyran compounds. Thus, no specific utility is described in the instant specification for the claimed invention.

19. Claims 66-74 and 86-88 are also rejected under 35 U.S.C. 112, first paragraph, enablement. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 66-69 and 86-87 are rejected under 35 U.S.C. § 102(b) as being anticipated by **GenBank Accession Number U65015** (*Vibrio furnissii* GlcNAc-6-P-deacetylase (manD), complete cds (1996)) **as evidenced by Kerr *et al.*** (*In Vitro* Biosynthetic Studies of the Bryostatins, Anti-Cancer Agents from the Marine Bryozoan *Bugula neritina*. Tetrahedron Letters (1996) 37(46):8305-8308). Claims 66-69 and 86-87 are drawn to nucleic acid molecules that encode a polypeptide involved in polyketide and/or bryopyran biosynthesis, wherein said nucleic acid molecules are native to a marine bacteria and wherein said nucleic acid molecules hybridize to SEQ ID NO:37. Claims 86-87 are included by virtue of the unclear hybridization limitations and any DNA will hybridize to any other DNA by virtue of its natural affinity.

GenBank Accession Number U65015 teaches the DNA sequence of N-acetylglucosamine-6-phosphate deacetylase from *Vibrio furnissii*, a marine bacterium. This deacetylase is well-known in the art to produce acetate; acetate is used as a precursor in both polyketide and bryostatin production (see Kerr *et al.*). Thus, the DNA sequence meets all the clear limitations of the instant claims.

Conclusion

21. Claims 66-74 and 86-88 are rejected for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK
March 4, 2003